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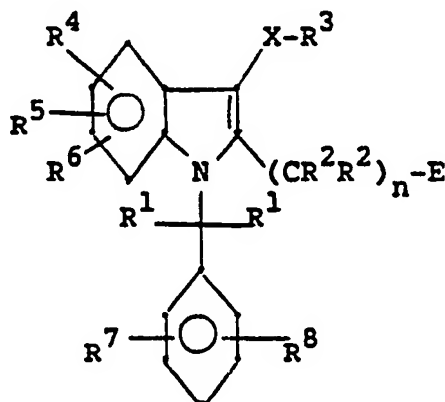
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⑤④ 3-hetero-substituted-N-benzyl-indoles.

⑤⑦ Compounds having the formula:



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are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-

3-HETERO-SUBSTITUTED-N-BENZYL-INDOLES

BACKGROUND OF THE INVENTION

5 The leukotrienes and their biological activities, especially their roles in various disease states and conditions have been described. For example, see EP 140,684 (May 8, 1985), which is incorporated herein by reference.

Several classes of compounds exhibit ability to inhibit the biosynthesis of leukotrienes in mammals, especially humans.

See, for example, EP 166,591 (January 2, 1986). The compounds of the present invention are distinguished from those of EP 166,591 in the important feature of possessing a heteroatom at position 3 in place of a hydrogen or carbon substituent. The heteroatom introduces unique electronic and chemical properties into the indole nucleus. The compounds of the present invention are further distinguished in that they uniquely inhibit the biosynthesis of leukotrienes, whereas those of EP 166,591 are antagonists of prostaglandins which also possess leukotriene biosynthesis inhibitory properties.

15 CH-A 454,858 and CH-A-455,777 teach derivatives of indole-2-acetic acid as useful for the treatment of inflammatory diseases. The compounds of these two Swiss patents are distinguished from those of the present invention by the same chemical differences as in EP 166,591, as well as by differences in the scope of their biological activities.

Walton *et al.*, J. Med. Chem., 11, 1252 (1968) teach certain indole-3-acetic acid derivatives assayed for tumor chemotherapy activity. Walton *et al.* teach compounds with an alkanolic acid in the 3-position, rather than in the 2-position, and they also lack a heteroatom substituent. The single compound of Walton *et al.* with a 2-alkanoic acid also lacks a 3-hetero substituent. Walton *et al.* disclose no useful biological activity for their indole 2-alkanoic acid.

25 JP-238017 teaches 3-substituted-2-phenyl-indole derivatives as having lipooxygenase and cyclooxygenase inhibiting activity. In addition to the important differences in biological activities, these compounds possess a phenyl group in the 2-position and are lacking the N-benzyl substituent of the compounds of the present invention.

30 SUMMARY OF THE INVENTION

The present invention relates to compounds having activity as leukotriene biosynthesis inhibitors, to methods for their preparation, and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

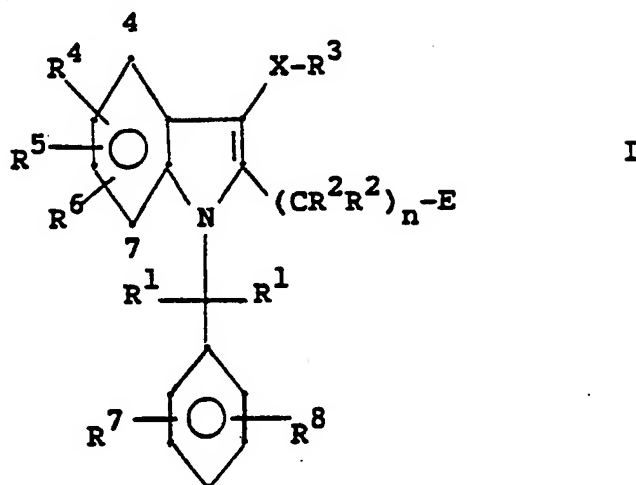
35 Because of their activity as leukotriene biosynthesis inhibitors, the compounds of the present invention are useful as anti-asthmatic, anti-allergic, and anti-inflammatory agents and are useful in treating allergic rhinitis and chronic bronchitis and for amelioration of skin diseases like psoriasis and atopic eczema. These compounds are also useful to inhibit the pathologic actions of leukotrienes on the cardiovascular and vascular systems for example, actions such as result in angina or endotoxin shock. The compounds of the present invention are useful in the treatment of inflammatory and allergic diseases of the eye, including allergic conjunctivitis. The compounds are also useful as cytoprotective agents and for the treatment of migraine headache.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; inflammatory bowel disease; ethanol-induced hemorrhagic erosions; hepatic ischemic; noxious agent induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as CCl₄ and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma-or stress-induced cell damage; and glycerol-induced renal failure.

50 The compounds of this invention are inhibitors of the biosynthesis of 5-lipoxygenase metabolites of arachidonic acid, such as 5-HPETE, 5-HETE and the leukotrienes. Leukotrienes B₄, C₄, D₄ and E₄ are known to contribute to various disease conditions such as asthma, psoriasis, pain, ulcers and systemic anaphylaxis. Thus inhibition of the synthesis of such compounds will alleviate these and other leukotriene-related disease states.

DETAILED DESCRIPTION

The compounds of this invention are best realized by Formula I:



wherein:

R¹ is H or loweralkyl;

R² is H or loweralkyl, or two R²'s may be joined to form a ring of 3-6 atoms;

R³ is alkyl, C₂-C₆ alkenyl, substituted or unsubstituted phenyl, -(CH₂)_m-Het, or M-substituted alkyl;

R⁴, R⁵ and R⁶ is each independently H, loweralkyl, C₂-C₆ alkenyl, or -(CR²R²)_pM;

R⁷ and R⁸ are independently H, C₁-C₃ alkyl, halogen, OH, CN, CF₃, C₁-C₃ alkoxy, C₁-C₃ alkylthio, CO₂H, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkylcarbonyl, or azide;

R⁹ is CF₃, loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

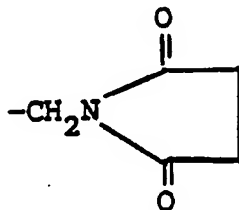
R¹⁰ is H, loweralkyl, unsubstituted phenyl, unsubstituted benzyl, or two R¹⁰'s attached to a nitrogen may form a ring of 5 to 7 members;

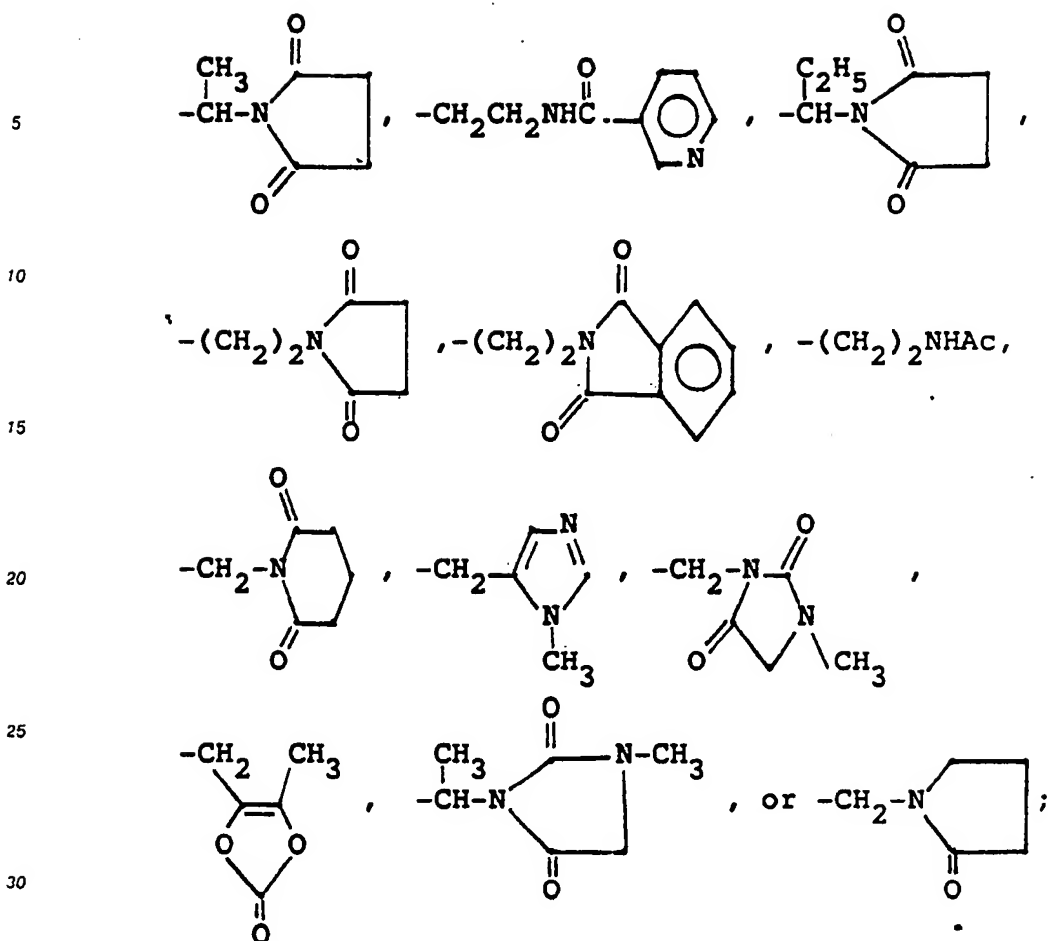
R¹¹ is H or -(CH₂)_qR⁹;

R¹² is loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

R¹³ is H, loweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl;

R¹⁴ is -CH₂CH₂N(R¹⁰)₂, CH₂CH(OH)CH₂OH, -CH₂O₂CC(CH₃)₃, -CH(CH₃)O₂CC(CH₃)₃.





E is CH_2OH , CO_2R^{13} , CO_2R^{14} , tetrazol-5-yl, CHO , $\text{C}(\text{O})\text{NR}^2\text{R}^2$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}^9$, or $\text{C}(\text{O})\text{N}(\text{OR}^2)\text{R}^2$;

M is a) OR^{10} ;


b) halogen;

c) CF_3 ;


d) SR^9 ;

e) substituted or unsubstituted phenyl;

f) COOR^{10} ;


g)  $\text{C}-\text{R}^{11}$;

h) tetrazole;

i)  $\text{NH}-\text{C}-\text{R}^{11}$;

j) $\text{NR}^{10}\text{R}^{10}$;

k) NHSO_2R^9 ;

l)  $\text{C}-\text{CH}_2\text{OH}$;


m) $\text{S}(\text{O})\text{R}^9$;


n) $\text{CONR}^{10}\text{R}^{10}$;

o) $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$;

p) $\text{S}(\text{O})_2\text{R}^9$;

q) NO_2 ;

r)  $\text{O}-\text{C}-\text{R}^{11}$;

s)  $\text{O}-\text{C}-\text{NR}^{13}\text{R}^{10}$;

- t) $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{OR}^2$;
 u) CN;
 v) N_3 ; or
 w) H;
 5 X is O, S, S(O), or S(O)₂;
 m is 0-2;
 n is 0-5;
 p is 0-3; and
 q is 0-4;
 10 and the pharmaceutically acceptable salts thereof.

Alkyl and alkenyl are intended to include linear, branched, cyclic, and linear cyclic (e.g., alkylcycloalkyl) structures.

As used herein, the term "alkyl" includes "loweralkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, norbornyl, undecyl, dodecyl, tridecyl, 15 tetradecyl, pentadecyl, eicosyl, 3-7-ethyl-2,2-methyl-4-propylnonyl, cyclododecyl, adamantyl and the like.

As used herein, the term "loweralkyl" includes those alkyl groups of from 1 to 7 carbon atoms. Examples of loweralkyl fragments include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

Alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, 20 cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl and the like.

As used herein, the term "alkoxy" includes those alkoxy groups of from 1 to 7 carbon atoms of either a straight, branched, or cyclic configuration. Examples of alkoxy fragments include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, pentyloxy, cycloheptyloxy, and the like.

Substituted phenyl and substituted benzyl include 1 or 2 substituents on the benzene ring selected 25 from C₁-C₃ alkyl, halogen, CN, CF₃, C₁-C₃ alkoxy, C₁-C₃ alkylthio, CO₂H, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkylcarbonyl and azide.

By "Het" is meant 2-, 3-, or 4-pyridyl; tetrazolyl; 2- or 3-thienyl; 2-, 4-, or 5-thiazolyl; 2-, 4-, or 5-thiazolinyl; 1-, 2-, 4-, or 5-imidazolyl; 3-[1,2,5]-thiadiazolyl; benzothiazol-2-yl; or 2-, 3-, or 4-quinolinyl, each 30 optionally substituted with 1 or 2 substituents selected from C₁-C₃ alkyl, halogen, CN, CF₃, C₁-C₃ alkoxy, C₁-C₃ alkylthio, CO₂H, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkylcarbonyl and azide.

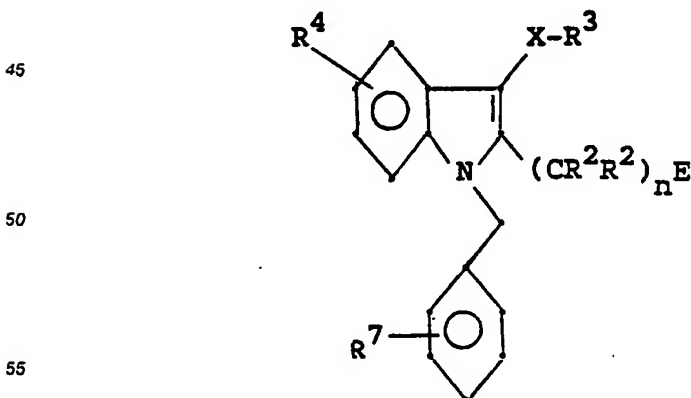
By "halogen" is meant F, Cl, Br, and I.

It is intended that the definitions of any substituent (e.g., R², R⁴, R⁵, etc.) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, -NR²R² represents -NHH, -NHCH₃, -NCH₂CH₃, etc.

35 Some of the compounds described herein contain one or more centers of asymmetry and may thus give rise to diastereoisomers and optical isomers. The present invention is meant to comprehend such possible diastereoisomers as well as their racemic and resolved, optically active forms. Optically active (R) and (S) isomers may be resolved using conventional techniques.

Some of the compounds described herein contain olefinic double bonds, and unless specified 40 otherwise, are meant to include both E and Z geometric isomers.

Preferred compounds of Formula I are represented by Formula Ia:

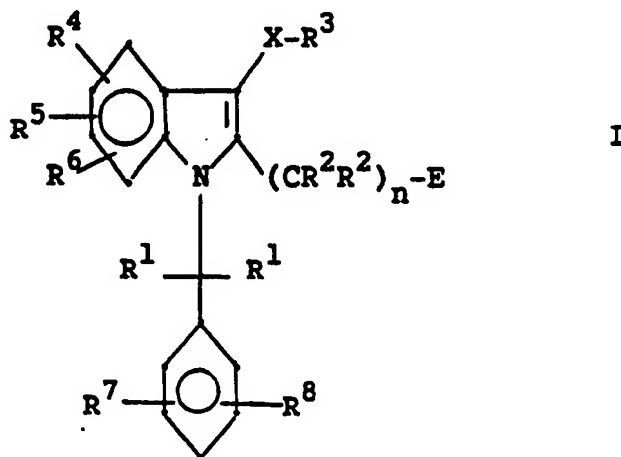


Ia

wherein:

Claims

1. A compound of the formula:



wherein:

R¹ is H or loweralkyl;

R² is H or loweralkyl, or two R²'s may be joined to form a ring of 3-6 atoms;

R³ is alkyl, C₂-C₆ alkenyl, substituted or unsubstituted phenyl, -(CH₂)_m-Het, or M-substituted alkyl;

R⁴, R⁵ and R⁶ is each independently H, loweralkyl, C₂-C₆ alkenyl, or -(CR²R²)_pM;

R⁷ and R⁸ are independently H, C₁-C₃ alkyl, halogen, OH, CN, CF₃, C₁-C₃ alkoxy, C₁-C₃ alkylthio, CO₂H, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkylcarbonyl, or azide;

R⁹ is CF₃, loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

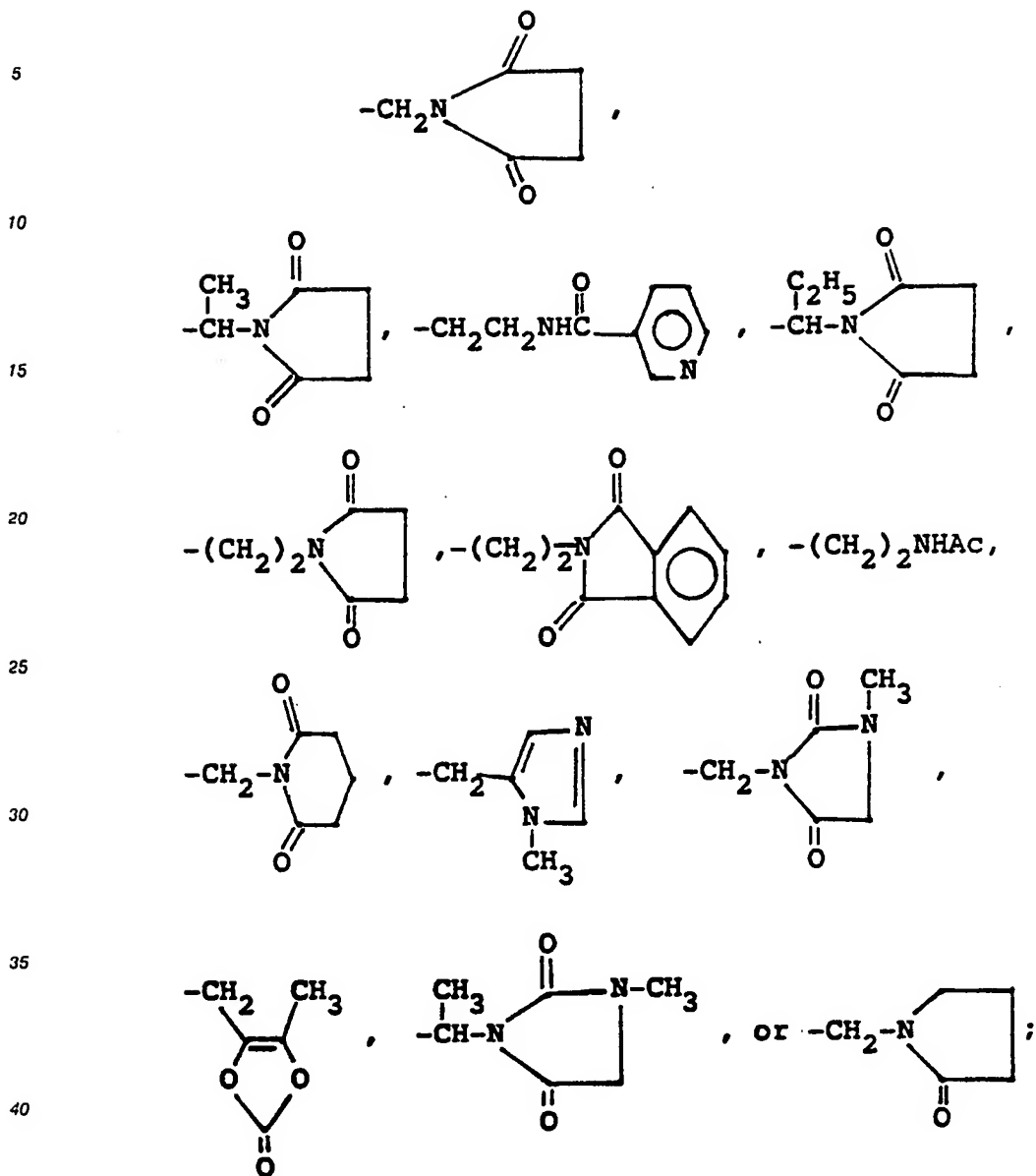
R¹⁰ is H, loweralkyl, unsubstituted phenyl, unsubstituted benzyl, or two R¹⁰'s attached to a nitrogen may form a ring of 5 to 7 members;

R¹¹ is H or -(CH₂)_qR⁹;

R¹² is loweralkyl, substituted or unsubstituted benzyl, or substituted or unsubstituted phenyl;

R¹³ is H, loweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted benzyl;

R¹⁴ is -CH₂CH₂N(R¹⁰)₂, CH₂CH(OH)CH₂OH, -CH₂O₂CC(CH₃)₃, -CH(CH₃)O₂CC(CH₃)₃.



E is CH_2OH , CO_2R^{13} , CO_2R^{14} , tetrazol-5-yl, CHO , $\text{C(O)NR}^2\text{R}^2$, $\text{C(O)NHS(O)}_2\text{R}^9$, or $\text{C(O)N(OR}^2\text{)R}^2$;

45 M is a) OR^{10} ;

b) halogen;

c) CF_3 ;

d) SR^9 ;

e) substituted or unsubstituted phenyl;

50 f) COOR^{10} ;

g) C(=O)-R^{11} ;

h) tetrazole;

55 i) -NH-C(=O)-R^{11} ;

j) $\text{-NR}^{10}\text{R}^{10}$;

k) $\text{-NHSO}_2\text{R}^9$;

- l) $-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2\text{OH}$;
 m) $-\text{S}(\text{O})\text{R}^9$;
 n) $-\text{CONR}^{10}\text{R}^{11}$;
 o) $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$;
 5 p) $-\text{S}(\text{O})_2\text{R}^9$;
 q) NO_2 ;
 r) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{11}$;
 10 s) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{10}\text{R}^{11}$;
 t) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}^{12}$;
 u) CN ;
 v) N_3 ; or
 15 w) H ;
 X is O, S, $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$;
 m is 0-2;
 n is 0-5;
 p is 0-3; and
 20 q is 0-4;

and the pharmaceutically acceptable salts thereof.

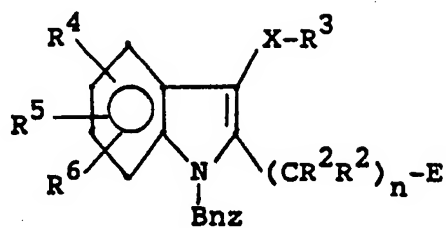
2. A compound of Claim 1 wherein the substituents are as follows:

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n$	E	X
1.	4-Cl-Bz	Ph	5-Cl	H	H	n=0	CO ₂ Et	S
2.	4-Cl-Bz	Ph	5-Cl	H	H	n=0	CO ₂ H	S
3.	4-Cl-Bz	Me	5-F	H	H	CH ₂	CO ₂ Et	S
4.	4-Cl-Bz	Me	5-F	H	H	CH ₂	CO ₂ H	S
5.	4-Cl-Bz	Me	5-F	H	H	CH ₂	CO ₂ H	SO ₂
6.	4-Cl-Bz	Me	5-F	H	H	CH(CH ₃)	CO ₂ H	S
7.	4-Cl-Bz	Me	5-F	H	H	C(CH ₃) ₂	CO ₂ H	S
8.	4-Cl-Bz	Ph	5-F	H	H	CH ₂	CO ₂ H	S
9.	4-Cl-Bz	Ph	5-F	H	H	CH(CH ₃)	CO ₂ H	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n-$	E	X
10.	4-Cl-Bz	Ph	5-i-Pr	H	H	CH ₂	CO ₂ H	S
11.	4-Cl-Bz	Ph	5-i-Pr	H	H	CH(CH ₃)	CO ₂ H	S
12.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH ₂	CO ₂ H	S
13.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH ₂	CO ₂ H	SO
14.	4-Cl-Bz	Ph	5-t-Bu	H	H	CH ₂	CO ₂ H	SO ₂
15.	4-Cl-Bz	Ph	5-F	H	H	(CH ₂) ₂	CO ₂ H	S
16.	4-Cl-Bz	Ph	5-i-Pr	H	H	(CH ₂) ₂	CO ₂ H	S
17.	4-Cl-Bz	Me	5-F	H	H	(CH ₂) ₂	CO ₂ H	S
18.	4-Cl-Bz	Ph	5-F	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2)_n-$	E	X
19.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
20.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
21.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO ₂
22.	4-Cl-Bz	Ph	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	S
23.	4-Cl-Bz	Me	5-F	H	H	$CH_2C(CH_3)_2$	CO_2H	S
24.	4-Cl-Bz	Me	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
25.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
26.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO
27.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO ₂

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n$	E	X
28.	4-Cl-Bz	t-Bu	5-Ph	H	H	$CH_2C(CH_3)_2$	CO_2H	S
29.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2C(CH_3)_2$	CO_2H	S
30.	4-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
31.	4-Cl-Bz	Me	5-F	H	H	$CH_2C(CH_3)_2$	CO_2H	O
32.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2$	CO_2H	O
33.	4-Cl-Bz	Me	5-F	H	H	$(CH_2)_2$	CO_2H	O
34.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CH_2OH	S
35.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	$CONH_2$	S
36.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CHO	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n$	E	X
37.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CONH- -SO ₂ Ph	S
38.	4-Cl-Bz	Ph	5-i-Pr	H	H	$(CH_2)_2$	tetrazol-5-yl	S
39.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
40.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO
41.	4-Cl-Bz	CH_2CH_2OH	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
42.	4-Cl-Bz	$C(CH_3)_2CH_2CO_2H$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
43.	4-Cl-Bz	$C(CH_3)_2CH_2CO_2Me$	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
44.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
45.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO

Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^n)_n^{2,2}$	E	X
46.	4-Cl-Bz	c-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
47.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
48.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO
49.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
50.	4-Cl-Bz	C(CH ₃) ₂ CH ₂ OH	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
51.	4-Cl-Bz	4-Me ₂ NCH ₂ -Ph-	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
52.	4-Cl-Bz	4-Me ₂ NCH ₂ -Ph-	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO
53.	4-Cl-Bz	4-Me ₂ NCH ₂ -Ph-	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
54.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n-$	E	X
55.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO
56.	4-Cl-Bz	t-Bu	5-c-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
57.	4-Cl-Bz	2-imidazol	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
58.	4-Cl-Bz	2-imidazol	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO
59.	4-Cl-Bz	2-imidazol	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
60.	4-Cl-Bz	4-imidazol	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
61.	4-Cl-Bz	2-(1-Me-imidazol)	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
62.	4-Cl-Bz	5-(1-Me-tetrazol)	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
63.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	$\overline{CH_2CCH_2CH_2}$	CO ₂ H	S

Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n-$	E	X
64.	4-Cl-Bz	4-pyridyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
65.	4-Cl-Bz	2-pyridyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
66.	4-Cl-Bz	2-thiazolyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
67.	4-Cl-Bz	2-thiazoliny]	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
68.	4-Cl-Bz	CH ₂ -2-pyridyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
69.	4-Cl-Bz	CH ₂ -4-pyridyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
70.	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	O
71.	4-Cl-Bz	t-Bu	5-Ph	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	O
72.	4-Cl-Bz	i-Pr	5-Ph	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	O

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Ex.	Bnz	R^3	R^4	R^5	R^6	$-(CR^2)_n^2$	E	X
73.	4-Cl-Bz	i-Pr	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	O
74.	4-MeOBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
75.	4-OHBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
76.	3-I, 4-OHBz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	SO_2
77.	3,4-di-Cl-Bz	t-Bu	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
78.	4-Cl-Bz	Ph	5-Et	H	7-Me	$CH_2C(CH_3)_2$	CO_2H	S
79.	4-Cl-Bz	Ph	6-i-Pr	H	H	$CH_2C(CH_3)_2$	CO_2H	S
80.	4-MeO-Bz	n-Bu	4-Me	H	6-i-Pr	$CH_2C(CH_3)_2$	CO_2H	SO_2
81.	4-Cl-Bz	t-Bu	5-OEt	H	H	$CH_2C(CH_3)_2$	CO_2H	S

Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2)_n-$	E	X
82.	2,6-di-Cl-Bz	Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
83.	4-Cl-Bz	t-Bu	5-i-Pr	H	7-Me	$CH_2C(CH_3)_2$	CO ₂ H	S
84.	3,5-di-Cl-Bz	Ph	5-i-Pr	H	6-Me	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
85.	4-Cl-Bz	4-MePh	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	O
86.	4,6-di-Cl-Bz	t-Bu	5-OMe	H	4-Me	$CH_2C(CH_3)_2$	CO ₂ H	S
87.	4-Cl-Bz	4-NH ₂ -Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
88.	4-Cl-Bz	4-N ₃ -Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S
89.	4-Cl-Bz	3-NH ₂ -Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	SO ₂
90.	4-Cl-Bz	3-NHAc-Ph	5-i-Pr	H	H	$CH_2C(CH_3)_2$	CO ₂ H	S

Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2R^2)_n-$	E	X
91.	4-Br-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO
92.	4-Br-Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
93.	4-Br-Bz	Ph	5-MeO	H	6-Me	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
94.	4-I-Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
95.	4-SMe-Bz	Ph	4-Me	5-i-Pr	7-Ac	CH ₂ C(CH ₃) ₂	CO ₂ H	S
96.	4-S(O) ₂ NMe ₂	4-CN-Ph	4-N ₃	5-OEt	7-OAc	CH ₂ C(CH ₃) ₂	COCH ₂ OH	S
97.	4-S(O) ₂ NMe ₂	4-Itz-Ph	4-N ₃	5-OEt	7-OAc	CH ₂ C(CH ₃) ₂	COCH ₂ OH	S
98.	4-Cl-Bz	Ph	5-C(OH)(CH ₃) ₂	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
99.	4-Cl-Bz	Ph	5-CH(CH ₃)CH ₂ OH	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
100.	4-Cl-Bz	t-Bu	5-C(OH)(CH ₃) ₂	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2)_n^2$	E	X
101.	4-Cl-Bz	t-Bu	5-CH(CH ₃)CH ₂ OH	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
102.	4-Cl-Bz	n-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
103.	4-Cl-Bz	n-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
104	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
105	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO
106	4-Cl-Bz	Cyclohexyl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
107	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CONHCH ₂ CO ₂ H	S
108	4-Cl-Bz	CH ₂ -c-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
109	4-Cl-Bz	CH ₂ -c-Pr	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CONHCH ₂ CO ₂ H	S
110	4-Cl-Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CONHCH ₂ CO ₂ H	SO ₂
111	4-Cl-Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CONHCH ₂ CO ₂ H	S

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Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2)_n^2$	E	X
112	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CON(Me) ₂	S
113	4-Cl-Bz	CH ₂ -c-Pr	5-i-Pr	H	H	CH ₂ C(Cl) ₂	CONH ₂	S
114	4-OH-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
115a	4-NO ₂ -Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ CH ₃	SO ₂
115b	4-NH ₂ -Bz	Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	SO ₂
116	4-Cl-Bz	5-Cl-Benzo- thiazol-2-yl	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
117	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH(CH ₃)	CO ₂ H	S
118	4-CH ₃ SO ₂ -Bz	t-Bu	5-i-Pr	7-Cl	H	CH ₂ C(CH ₃) ₂	CO ₂ H	S
119	4-Cl-Bz	CH ₂ -c-Pr	5-i-Pr	4-CF ₃	7-Br	CH ₂ C(CH ₃) ₂	CO ₂ H	O
120	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₂	CO ₂ H	O

Ex.	Bnz	R ³	R ⁴	R ⁵	R ⁶	$-(CR^2)^n$	E	X
121	4-Cl-Bz	2-Quinoliny	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S
122	4-Cl-Bz	t-Bu	5-i-Pr	4-SEt	H	CH ₂ C(CH ₃) ₃ ²	CH ₂ OCOCH ₂ CO ₂ H	S
123	4-Cl-Bz	t-Bu	5-i-Pr	7-COMe	H	CH ₂ C(CH ₃) ₃ ²	CH ₂ NHCOCH ₂ CO ₂ H	S
124	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ² -CH ₂	CO ₂ H	S
125	4-MeO-Bz	4-N ₃ -Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	SO ₂
126	3-CN-Bz	t-Bu	5-i-Pr	4-S(O) ₂ -Me	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S
127	4-Cl-Bz	CH ₂ CH=CH ₂	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S
128	4-Cl-Bz	Bz	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S
129	4-Cl-Bz	2-(i-Pr)Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S
130	4-Cl-Bz	2-(i-Pr)Ph	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	SO ₂
131	4-Cl-Bz	t-Bu	5-i-Pr	H	H	CH ₂ C(CH ₃) ₃ ²	CO ₂ H	S

3. The compounds of Claim 1 which are:

- ethyl 1-(p-chlorobenzyl)-5-chloro-3-thiophenylindole-2-carboxylate;
 1-(p-chlorobenzyl)-5-chloro-3-thiophenylindole-2-carboxylic acid;
 ethyl 1-(p-chlorobenzyl)-5-fluoro-3-methylthioindole-2-acetate;
 1-(p-chlorobenzyl)-5-fluoro-3-methylthioindole-2-acetic acid;
 1-(p-chlorobenzyl)-5-fluoro-3-methylsulfonylindole-2-acetic acid;
 1-(p-chlorobenzyl)-5-fluoro- α -methyl-3-methylthioindole-2-acetic acid;
 1-(p-chlorobenzyl)- α , α -dimethyl-5-fluoro-3-methylthioindole-2-acetic acid;
 1-(p-chlorobenzyl)-5-fluoro-3-phenylthioindole-2-acetic acid;
 1-(p-chlorobenzyl)-5-fluoro- α -methyl-3-phenylthioindole-2-acetic acid;
 1-(p-chlorobenzyl)-3-phenylthio-5-(i-propyl)-indole-2-acetic acid;
 1-(p-chlorobenzyl)- α -methyl-3-phenylthio-5-(i-propyl)-indole-2-acetic acid;
 1-(p-chlorobenzyl)-5-(t-butyl)-3-phenylthio-indole-2-acetic acid;
 1-(p-chlorobenzyl)-5-(t-butyl)-3-phenylsulfinylindole-2-acetic acid;